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Is antibiotic prophylaxis necessary for anterior epistaxis with packing? Insights from a large database

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ABSTRACT

Introduction: Patients with spontaneous epistaxis frequently receive anterior nasal packing (ANP) when bleeding is not controlled by other measures in the emergency department (ED). Many patients also receive prophylactic antibiotics (Abx), although the evidence about their benefits mostly derived from small studies, is unclear. This study aimed to leverage a large international database to investigate the prevalence of clinically significant infection (CSI) among patients with ANP who received prophylactic Abx.

Methods: This is a retrospective analysis from TriNetX which includes 130 million patients. All adult patients who underwent ANP for spontaneous epistaxis were eligible. The intervention was prophylactic Abx within one day of the index ED visits; outcomes were 30-day rate of CSI, and adverse drug events (ADE). We utilized TriNetX's propensity score matching using demographic and clinical variables to match patients prior to comparing their outcomes.

Results: 6302 patients were eligible for analysis, mean age (±SD) for both groups was 65 (±19 years), 42 % being female. The CSI analysis included 5487 patients, 2737 (50 %) receiving Abx. Total rate of CSI was 25 (0.45 %) patients, 15 (0.5 %) among patients with prophylactic Abx compared with 10 (0.4 %) CSI for those without Abx (Risk Difference 0.2 %, 95 % CI -0.005 to 0.002, $p = 0.31$). There were 26 (1 %) patients with ADE per group (Risk Difference 0, 95 % CI -0.005 to 0.006, $p = 0.94$).

Conclusion: The results from this large group of patients demonstrated that the rates of CSI and ADE among patients with anterior nasal packing for spontaneous epistaxis were low. We recommend against the practice of prophylactic antibiotics in anterior nasal packing, since the practice provides little benefit while posing a potential risk to the population.

1. Introduction

In the United States, anterior epistaxis accounts for up to 90 % of emergency department (ED) visits for the chief complaint of "nosebleed" [1]. Initial treatment for anterior epistaxis includes direct pressure, topical vasoconstrictors, and cauterization [2]. If these conservative measures are unsuccessful then nasal packing is the treatment of choice to provide hemostasis. Up to 20 % of patients with epistaxis will require such packing [3].

Clinicians may also prescribe antibiotics for patients treated with nasal packing for anterior epistaxis to prophylactically prevent toxic shock syndrome, sinusitis, and otitis media, although this practice is controversial [4]. A meta-analysis of 383 patients suggested that the rate of clinically significant infection (CSI) was not statistically significant between patients who received prophylactic antibiotics and those who did not after undergoing nasal packing [4]. Due to the rising rate of unnecessary antibiotic prescriptions in the United States, the risk of antibiotic resistance is increasing, and so are the associated costs [5,6]. There is an urgent need to avoid unnecessary antibiotics, including for

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patients with anterior nasal packing when the benefit for antibiotics is unclear. The majority of studies regarding rates of CSI among patients with anterior nasal packing involved small sample sizes that ranged from 28 patients to 149 patients. Overall, the evidence suggested that there was no difference in CSI rates between patients who received prophylactic antibiotics versus those who did not. The similar rates of CSI could be, in part, due to the small sample sizes of the studies and the low prevalence of the disease states. Additionally, all of the studies were observational and, due to their small sample size, no advanced statistical analyses were performed to compare balanced groups of patients who received prophylactic antibiotics to patients who did not receive prophylactic antibiotics.

This study aimed to use a large database to investigate the rates of CSI in patients who received prophylactic antibiotics and those who did not. Through a larger sample size of patients and via a more rigorous propensity matching method, this study aimed to produce a balanced population of patients who underwent nasal packing for anterior epistaxis. We hypothesized that, similar to previous studies, the rate of CSI would be similar between patients who did and did not receive prophylactic antibiotics. Investigating this question will provide further evidence to help clinicians with their decision making when treating patients with anterior epistaxis that requires nasal packing.

2. Methods

2.1. Design

This retrospective, propensity-matched cohort study was completed using the TriNetX database (https://trinetx.com/) over the 20-year period from December 10, 2004 through December 10, 2024. TriNetX includes data from 94 different large health care organizations (HCOs) with over 130 million patient records across five countries in the Americas, Europe, and Asia. The database includes de-identified health records for admissions, discharges, and office visits. These records include patient diagnoses, laboratory values, demographic data, procedure information, and pharmacological treatments. To provide a common structured and uniform dataset, all of the data from different countries and different HCOs are mapped to commonly agreed upon terminologies when they are imported into TriNetX. Within TriNetX, diagnoses use International Classification Definition (ICD), ICD and Current Procedural Terminology (procedures), RxNorm (medications), Logical Observation Identifiers Names and Codes (LOINCs)—for laboratory test results [7].

2.2. Participants

Our study was designed using the PICO [P – Patient, problem, or population; I – Intervention; C – Comparison, control, or comparator; O – Outcome(s)] format. First, all adult patients between ages 18 and 90 years old who presented to any ED with an epistaxis diagnosis (ICD10CM:R04.0) that were controlled with anterior nasal packing (ICD9CM:21.01 or ICD10PCS:2Y41X5Z) were eligible for the study.

The intervention was determined by the presence of antibiotic treatment within one day of the index ED visit. Antibiotics in the intervention group included, clindamycin, trimethoprim- sulfamethoxazole, amoxicillin-clavulanate, and cephalexin, as they were commonly used for this condition [4,8]. Individuals were excluded if they were documented as having posterior nasal packing or having received cautery (CPT:30905) at any point since we could not ascertain for what type of bleeding this procedure was performed for. The control cohort was defined as all patients with a diagnosis of epistaxis with anterior nasal packing, who did not receive any of the aforementioned antibiotics within one day of the index ED visit. The full list of the inclusion and exclusion criteria is included in Appendix 1. Patients were also excluded in both groups if they had any of the outcome measures (any clinically significant infection, any adverse drug event as defined in the Outcome subsection) prior to the index ED visit for epistaxis.

This study was considered non-human subject research by our Institution Review Board. Therefore, formal consent was exempted.

2.3. Outcome measurements

The primary outcome of interest was the 30-day rate of CSI. These CSIs were defined as sinusitis (ICD10CM:J01, HCPCS:G9364), otitis media (ICD10CM:H66.9), cellulitis of the face (ICD10CM:L03.211), and toxic shock syndrome (ICD10CM:A48.3). These infections have been used in previous studies [4]. The secondary outcome was the 30-day rate of adverse drug-related events. These events were identified by TriNetX as "unspecified adverse events of drug or medicament," "adverse effect of penicillin, initial counter," "any diarrhea," and "*Clostridium difficile* infection."

2.4. Statistical analysis

Statistical analysis, including descriptive and outcomes analyses, was performed via the TriNetX platform. Descriptive statistics were presented as mean ± standard deviation (SD), or frequency (percent, %). The TriNetX platform's propensity-score matching tool was utilized to match patients who did receive antibiotics versus those who did not receive antibiotics. Cohorts were matched according to age, sex, ethnicity, past medical history, vital signs (blood pressure, heart rate, respiratory rate, oxygen saturation) at ED triage, and laboratory values. The comprehensive list of 80 parameters that were used for the propensity score matching is available in Appendix 2. The TriNetX propensity score uses logistic regressions, and the specified covariates to provide the propensity score, which is reported by TriNetX as the Standardized Difference (Std. Diff.), for each patient for their likelihood to be included in the specified cohort [9]. TriNetX then uses "greedy nearest neighbor matching" with a caliper of 0.1 to match patients as 1:1 pairs, according to their propensity score.

To test our hypotheses, univariate statistical analysis with Student's *t*-tests were completed in TriNetX. Comparisons of outcomes between propensity score matched groups were expressed as Risk Difference, the 95 % confidence interval (95 % CI), and the associated *p*-values. The Chi-square test was performed via Minitab version 21 (www.minitab.com, State College, Pennsylvania, USA). All tests with p-value <0.05 were considered statistically significant.

3. Results

3.1. Patient demographics

The query identified a total of 15,224 patients before propensity score matching, 3161 (21 %) patients were identified as having received antibiotics (Fig. 1). The propensity score matching identified a total of 6302 patients (3151 patients for each group). The mean age (± Standard Deviation [SD]) for both groups was 65 (± 19 years); 42 % were female. Thirty-one (31 %) of the patient population in both groups had a past medical history of diabetes mellitus, and 70 % had hypertensive diseases (Table 1).

For analysis of CSI rate, 401 patients in the control group (without prophylactic antibiotics) and 414 patients who were given prophylactic antibiotics were excluded from results because they had those outcomes prior to the index ED visit. As a result, 5487 patients were included in the analysis, 2750 (50 %) patients did not receive prophylactic antibiotics while 2737 (50 %) received prophylactic antibiotics (Fig. 1). Similarly, for the analysis of adverse events, 635 patients in

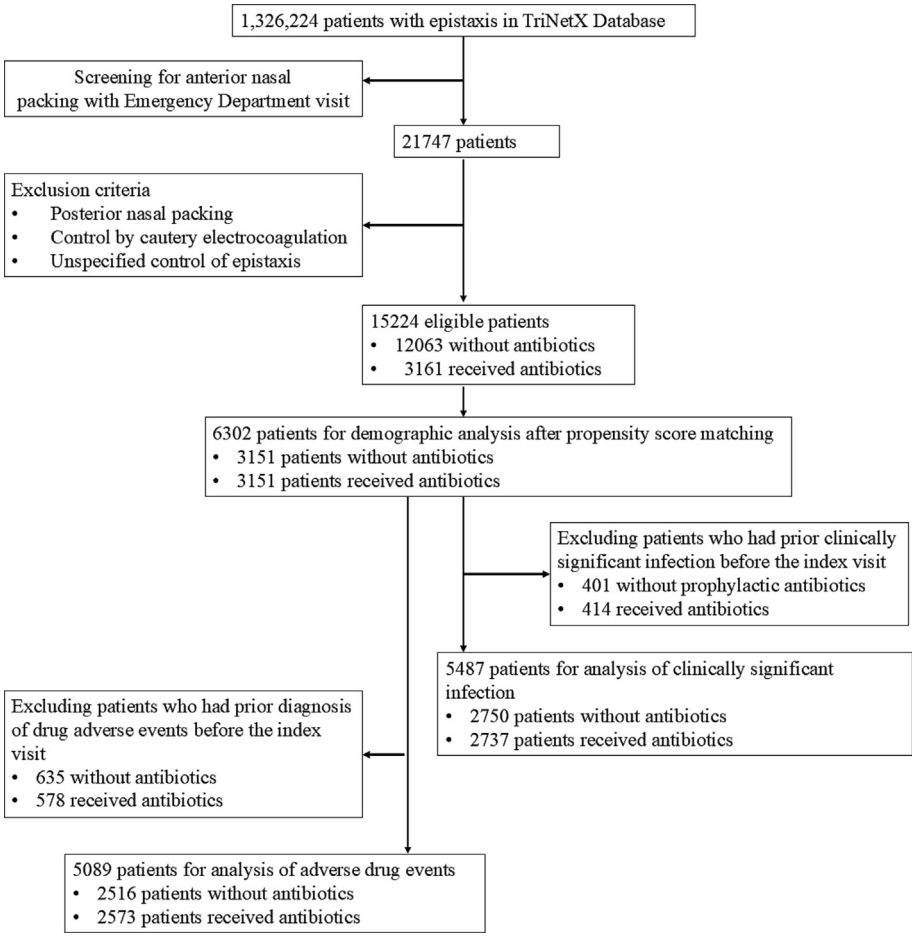

Fig. 1. Flow diagram depicting patient selection and final population included in the analysis.

the control group (without prophylactic antibiotics) and 578 patients who were given prophylactic antibiotics were excluded before the start of the analysis because they had the outcomes prior to the index ED visit. Therefore, 5089 patients were included in the analysis for adverse drug events, 2516 (49 %) patients did not receive prophylactic antibiotics, and 2573 (51 %) patients received prophylactic antibiotics (Fig. 1).

Due to the large sample size, some of the characteristics were statistically different, but not clinically different between the groups. For example, systolic blood pressure was 128 (± 24) millimeters of mercury (mmHg) for those without antibiotics and 130 (± 24) ($p < 0.001$) for those receiving antibiotics. The mean International Normalized Ratio (INR) was 1.5 (± 1.0) for those without antibiotics and 1.6 (± 1.1, $p < 0.001$) for those with antibiotics.

The mean (± SD) hemoglobin level was 11.6 (± 3) gram/deciliter for those without antibiotics vs. 12 (±3, $P < 0.001$) for those with antibiotics. The platelet counts were 221 (± 107) (count per microliter) for patients without antibiotics and 222 (± 101, $p = 0.68$) for those with antibiotics (Table 1). All other demographic and clinical factors were similar in both groups.

3.2. Primary outcome

The overall prevalence of CSI was 25 (0.5 %) in this patient population (Table 2). There were 10 (0.4 %) patients with a CSI within the group who did not receive prophylactic antibiotics, compared with 15 (0.5 %) patients in the group that received prophylactic antibiotics (Risk Difference 0.6 %, 95 % CI -0.013 to 0.001, $p = 0.31$) (Table 2).

3.3. Secondary outcome

The overall prevalence of any adverse drug event was 1 % (52/5487). There were 26 (1 %) patients in each group who had any adverse events (Table 2). The risk difference was 0 % (95 % CI -0.005 to 0.006, $p = 0.94$) (Table 2).

4. Discussion

This study investigated the rate of CSI between patients who underwent anterior nasal packing for epistaxis and received antibiotics versus those who underwent anterior nasal packing for epistaxis but did not receive antibiotics. The study demonstrated that the rate of CSI was low overall (0.5 %) and that there was no statistically significant difference between the rates of CSI for both groups. Furthermore, there was a small rate of adverse drug events (1 %) among patients, although the rate was similar between the groups.

The overall rate of CSI at 30-day follow-up from our study was low (1.2 %). The low prevalence of CSI from this study was in agreement with a previous meta-analysis which reported the overall rate of CSI at 0.8 % [4]. However, the range of follow-ups from previous studies varied from 7 days to 6 weeks with some studies not even reporting the length of follow-up. Therefore, this study provided a good framework for future researchers to establish reasonable follow-up intervals.

Additionally, most of the previous studies did not explicitly report the rates of CSI between the groups with and without antibiotics, most likely because their sample sizes were small. This study, however,

Table 1
Demographic and clinical characteristics of patients after propensity score matching, with anterior epistaxis and nasal packing. Only common clinical variables are presented here.

	Without Antibiotics n = 3151	With Antibiotics *n* = 3151	Std Diff	P-Value
Age At Index				
Age, Mean ± SD	65.7 ± 20.5	65.1 ± 18.6	0.034	0.172
Sex, n(%)				
Male	1657 (56.8 %)	1666 (57.1 %)	0.006	0.812
Female	1331(42.2 %)	1311 (41.6 %)	0.013	0.61
Ethnicity, n(%)				
Not Hispanic or Latino	2579 (81.8 %)	2543 (80.7 %)	0.029	0.245
Hispanic or Latino	125 (4.0 %)	145 (4.6 %)	0.031	0.213
Race, n(%)				
White	2308 (73.2 %)	2282 (72.4 %)	0.019	0.462
Black or African American	370 (11.7 %)	369 (11.7 %)	0.001	0.969
Asian	146 (4.6 %)	131 (4.2 %)	0.023	0.357
Other	80 (2.5 %)	101 (3.2 %)	0.04	0.113
Unknown	213 (6.8 %)	226 (7.2 %)	0.016	0.52
Native Hawaiian or Other Pacific Islander	25 (0.8 %)	31 (1.0 %)	0.02	0.421
American Indian or Alaska Native	10 (0.3 %)	11 (0.3 %)	0.006	0.827
Past medical history, n(%)				
Hypertensive Diseases	1927 (61.2 %)	1906 (60.5 %)	0.014	0.588
Acute Kidney Failure and Chronic Kidney Disease	912 (28.9 %)	899 (28.5 %)	0.009	0.717
Diseases of Liver	425 (13.5 %)	406 (12.9 %)	0.018	0.479
Laboratory Values				
WBC	8.2 ± 5.2	8.8 ± 11.1	0.07	0.029
Hemoglobin [g/dL]	11.6 ± 2.5	12.0 ± 2.5	0.145	<0.001
Hematocrit [Volume Fraction]	35.1 ± 7.1	36.2 ± 7.1	0.143	<0.001
Platelets [g/dL]	220.6 ± 106.7	221.8 ± 101.5	0.012	0.688
Sodium [mmol/L]	138.1 ± 3.9	138.2 ± 3.6	0.012	0.672
Potassium [mmol/L]	4.1 ± 0.5	4.1 ± 0.5	0.045	0.125
Chloride [mmol/L]	102.2 ± 5.4	102.3 ± 4.8	0.023	0.42
Bicarbonate [mmol/L]	26.4 ± 4.2	26.4 ± 3.9	0.001	0.975
Urea Nitrogen [mg/dL]	24.1 ± 18.5	23.1 ± 16.2	0.056	0.021
Creatinine [mg/dL]	1.3 ± 1.3	1.3 ± 1.5	0.033	0.265
Glucose [mg/dL]	117.3 ± 42.9	120.1 ± 44.6	0.065	0.027
Activated Partial Thromboplastin Time (aPTT)	35.7 ± 16.0	35.2 ± 15.8	0.031	0.376
Prothrombin time (PT)	16.3 ± 7.7	17.1 ± 10.6	0.091	0.006
INR	1.5 ± 0.8	1.6 ± 1.1	0.121	<0.001
Aspartate Aminotransferase [U/L]	34.1 ± 46.9	33.7 ± 36.1	0.011	0.714
Alanine Aminotransferase[U/L]	28.3 ± 59.8	29.1 ± 32.4	0.015	0.617
Alkaline Phosphatase [U/L]	99.5 ± 76.8	98.8 ± 73.5	0.008	0.792
Vital Signs				
Blood Pressure, Systolic [mm Hg]	127.5 ± 24.1	130.1 ± 24.1	0.108	<0.001
Blood Pressure, Diastolic [mm Hg]	70.4 ± 14.0	72.2 ± 14.9	0.126	<0.001
Heart Rate [beats/min]	78.1 ± 16.8	78.5 ± 17.0	0.023	0.494
Respiratory Rate [breaths/min]	17.6 ± 3.3	17.4 ± 3.0	0.044	0.299
Oxygen Saturation (percentage)	88.0 ± 18.6	87.3 ± 20.1	0.038	0.454
BMI [kg/m^2]	28.5 ± 7.3	29.0 ± 7.4	0.063	0.032

beats/min, beats per minute; breaths/min, breaths per minute; g/dL, gram per deciliter; INR, International Normalized Ratio; kg/m2, kilogram per square meter; mg/dL, milligram per deciliter; mmol/L, millimole per liter; mm Hg, millimeter of mercury; s, seconds; U/L, units per liter; WBC, white blood cell counts.

was able to detect a number of CSI and further demonstrate that there was no difference between these groups. From our population, the absolute risk difference was 0.2 % between the group receiving prophylactic antibiotics and those who did not. From our calculation, the number needed to treat (NNT) to prevent one CSI was high at 500 (Appendix 3).

Previous literature suggested that immunocompromised patients should receive prophylactic antibiotics for anterior nasal packing [10]. Yet, there is no clear evidence as to whether patients with immunocompromised state is associated with a higher risk of having CSI when not receiving prophylactic antibiotics while having anterior nasal packing. A retrospective study involving a total of 275 patients with nasal packing for epistaxis reported that almost all immunocompromised patients (6 % of the total population) did not receive any prophylactic antibiotics, while up to 41 % of patients with history of diabetes received prophylactic antibiotics [11]. Nonetheless, there was no report of toxic shock syndrome nor acute sinusitis among any of the immunocompromised patients without prophylactic antibiotics [11].

The risk of antibiotic resistance has been on the rise over the years [12]. The cost from antibiotic resistance among inpatients in the United States has been estimated to be $4.6 billion annually [11]. Antibiotic stewardship to combat this trend is critical. This study demonstrated that there were no statistically significant adverse events in either group of patients whether they received antibiotics or not. Although this study may or may not be able to establish a direct association between these adverse events with the prescription of antibiotics, there was still a small risk of adverse events in the patient population.

The post-hoc power calculation for CSI, using G*Power [13], for our results to detect the difference of CSI between groups was 30 %, despite having a sample size of greater than 5000 patients. Due to the low prevalence of CSI, it's probable that the need for an exceptionally large sample size to achieve adequate power suggests that potential benefits may likely be minimal and does not justify routine antibiotic administration. Nonetheless, this study's findings provide further evidence to support other professional societies' guidelines regarding prophylactic

Table 2
Rates of clinically significant infections (CSI) and adverse drug events between patients with nasal packing with or without prophylactic antibiotics.

	Without Antibiotics	With Antibiotics	Risk Difference (95 % CI)	P-Value	Number Needed to Treat
CSI, n(%)[1]	10 (0.36 %)	15 (0.55 %)	0.002 (−0.005,0.002)	0.311	500
Adverse drug events, n (%)[2]	26 (1.01 %)	26 (1.01 %)	0.000 (−0.005,0.006)	0.935	NA

[1] For the analysis of CSI rate, 401 patients in the control group (without prophylactic antibiotics) and 414 patients who were given prophylactic antibiotics were excluded from results because they had the outcome prior to the index ED visit.
[2] For the analysis of adverse reaction, 635 patients in the control group (without prophylactic antibiotics) and 578 patients who were given prophylactic antibiotics were excluded from results because they had the outcome prior to the index ED visit.

antibiotics for anterior nasal packing. The American Academy of Otolaryngology–Head and Neck Surgery's clinical guidelines in 2020 [3], which were endorsed by the American College of Emergency Physician, did not mandate routine prophylactic antibiotics, due to the lack of evidence. However, this guideline also recommended individualization of antibiotics according to patients' risks of infection. Similarly, the organization Emergency Care of British Columbia [14] also does not support routine use of topical or oral antibiotics, but recommended antibiotics for patients with increased risk of infection or posterior packing. Thus, both societies do not rule out antibiotics for patients who are considered high risk. In contrast, the American Association for the Surgery of Trauma Critical Care Committee's clinical consensus document [15] does not recommend prophylactic antibiotics in the setting of nasal packing for traumatic epistaxis, citing a lack of evidence demonstrating benefit. Thus, our results mostly support those guidelines.

4.1. Limitations

There are several limitations that are relevant to this work. Although we matched patients in both groups with an extensive list of variables, even including a few common tumor markers, we could not ascertain each patient's immune status. Future studies should delve into this topic with greater granularity to determine the true impact a patient's immune status has on the risk of CSI with anterior nasal packing. The rigorous matching process likely caused the included patient population to be smaller and may not represent the general population well. Nonetheless, the patient population in this study was still significantly larger than in any previous studies. Additionally, the database encompassed healthcare organizations from outside the United States, which should be used to contextualize the findings. Global practice patterns regarding prophylactic antibiotic use for anterior nasal packing may differ from clinicians in the United States. Although using the diagnosis codes is a validated method to identify disease states, it may not accurately capture all cases of CSI or cases of adverse drug events. The contributing HCO may not be able to capture patient compliance with antibiotics or those who presented to facilities outside of the network for their CSI or ADE. Thus, they may not accurately capture the rate of CSI or ADEs. Additionally, one factor that might affect the rate of toxic shock syndrome was the rate of Staph Aureus Nasal Carriage (ICD-10 Z22.3221). However, this code was active in October 2024 so it could not be used in our study, which ended in December 2024. Finally, the data from TriNetX did not specify the types of nasal packing (absorbable versus non-absorbable), the duration of packing, length of treatment which might serve as an influential factor in the decision-making process to consider antibiotics as part of management.

5. Conclusion

Using a large, balanced group of patients, we demonstrated that the rate of clinically significant infection and adverse drug events among patients with anterior nasal packing for spontaneous epistaxis was low. Given the lack of significant benefit, the low incidence of infectious complications, and the importance of antibiotic stewardship, there is very little benefit of prophylactic antibiotics to most patients, while posing a potential risk to the overall population. Therefore, we recommend against the routine use of prophylactic antibiotics in clinical practice. Future studies with larger datasets may further refine risk stratification and capture the ideal timing and duration of packing.

Financial disclosure statement

The authors do not have any financial disclosures relevant to this manuscript.

Ethical approval/informed consent

This study was considered non-human subject research by our Institution Review Board (HP-00113013). Therefore, formal consent was exempted.

CRediT authorship contribution statement

Quincy K. Tran: Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Conceptualization. **Isha Vashee:** Writing – review & editing, Writing – original draft, Visualization, Investigation, Formal analysis, Data curation. **Rohan Vanga:** Writing – review & editing, Writing – original draft, Visualization, Investigation, Formal analysis, Data curation. **Samantha Camp:** Writing – review & editing, Writing – original draft, Visualization, Investigation. **Melissa K. Rallo:** Writing – review & editing, Writing – original draft, Visualization, Investigation. **Daniel Najafali:** Writing – review & editing, Writing – original draft, Project administration, Investigation. **Laura J. Bontempo:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Conceptualization. **Ali Pourmand:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Conceptualization.

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Declaration of competing interest

The authors have no competing interests relevant to the subject matter in this manuscript.

Appendix A. Appendix

Appendix 1. Inclusion and exclusion criteria for the query for patients who have spontaneous epistaxis and anterior nasal packing.

	Inclusion	Exclusion
Cohort lacking antibiotics	Epistaxis (UMLS:ICD10CM:R04.0)	Any instance of Antibiotics within 1 day on or after any instance of Diagnosis: clindamycin (NLM:RXNORM:2582); or sulfamethoxazole (NLM:RXNORM:10180); or trimethoprim (NLM:RXNORM:10829); or clavulanate (NLM:RXNORM:48203); or amoxicillin (NLM:RXNORM:723); or cephalexin (NLM:RXNORM:2231); or penicillin G (NLM:RXNORM:7980); or penicillin V (NLM:RXNORM:7984); or azithromycin (NLM:RXNORM:18631).
	Packing of Nasal Region using Packing Material (UMLS:ICD10PCS:2Y41X5Z)	Control nasal hemorrhage, posterior, with posterior nasal packs and/or cautery, any method; initial (UMLS:CPT:30905)
	Control of epistaxis by anterior nasal packing (UMLS:ICD9CM:21.01)	
	Visit: Emergency (UMLS:HL7V3.0:VisitType:EMER)	
Cohort with specific Antibiotics	Epistaxis (UMLS:ICD10CM:R04.0)	Control nasal hemorrhage, posterior, with posterior nasal packs and/or cautery, any method; initial (UMLS:CPT:30905)
	Packing of Nasal Region using Packing Material (UMLS:ICD10PCS:2Y41X5Z)	
	Control of epistaxis by anterior nasal packing (UMLS:ICD9CM:21.01)	
	Visit: Emergency (UMLS:HL7V3.0:VisitType:EMER)	
	Any instance of Antibiotics within 1 day on or after any instance of Diagnosis: clindamycin (NLM:RXNORM:2582); or sulfamethoxazole (NLM:RXNORM:10180); or trimethoprim (NLM:RXNORM:10829); or clavulanate (NLM:RXNORM:48203); or amoxicillin (NLM:RXNORM:723); or cephalexin (NLM:RXNORM:2231); or penicillin G (NLM:RXNORM:7980); or penicillin V (NLM:RXNORM:7984); or azithromycin (NLM:RXNORM:18631).	

Appendix 2. Results from the propensity matching between patients who received and did not receive antibiotics. This table contains all variables that were used for the propensity matching between both groups. Cohort 1 (Without Antibiotics) ($N = 3151$) and Cohort 2 (With Antibiotics) ($N = 3151$) characteristics after propensity score matching.

Cohort 1 ($N = 3151$) and cohort 2 ($N = 3151$) characteristics after propensity score matching [1]

Demographics

Variables	Cohort	Mean ± SD	Patients	% of Cohort	P-Value	Std diff.
Current Age	1	73.5 +/− 19.2			0.153	0.036
	2	72.8 +/− 17.4				
Age at Index	1	65.7 +/− 20.5			0.172	0.034
	2	65.1 +/− 18.6				
Female	1		1331	42.2 %	0.61	0.013
	2		1311	41.6 %		
Black or African American	1		370	11.7 %	0.969	0.001
	2		369	11.7 %		
Male	1		1788	56.7 %	0.665	0.011
	2		1805	57.3 %		
White	1		2308	73.2 %	0.462	0.019
	2		2282	72.4 %		
American Indian or Alaska Native	1		10	0.3 %	0.827	0.006
	2		11	0.3 %		
Unknown Race	1		213	6.8 %	0.52	0.016
	2		226	7.2 %		
Native Hawaiian or Other Pacific Islander	1		25	0.8 %	0.421	0.02
	2		31	1.0 %		
Unknown Gender	1		32	1.0 %	0.713	0.009
	2		35	1.1 %		
Not Hispanic or Latino	1		2579	81.8 %	0.245	0.029
	2		2543	80.7 %		
Hispanic or Latino	1		125	4.0 %	0.213	0.031
	2		145	4.6 %		
Other Race	1		80	2.5 %	0.113	0.04
	2		101	3.2 %		
Asian	1		146	4.6 %	0.357	0.023
	2		131	4.2 %		

Diagnosis

Variables	Cohort	Mean ± SD	Patients	% of Cohort	P-Value	Std diff.
Diabetes mellitus	1		857	27.2 %	0.712	0.009
	2		844	26.8 %		
Diseases of liver	1		425	13.5 %	0.479	0.018
	2		406	12.9 %		

(continued on next page)

(*continued*)

Cohort 1 (N = 3151) and cohort 2 (N = 3151) characteristics after propensity score matching [1]

Demographics						
Variables	Cohort	Mean ± SD	Patients	% of Cohort	P-Value	Std diff.
Chronic lower respiratory diseases	1		1019	32.3 %	0.223	0.031
	2		974	30.9 %		
Disorders of thyroid gland	1		586	18.6 %	0.58	0.014
	2		569	18.1 %		
Hypertensive diseases	1		1927	61.2 %	0.588	0.014
	2		1906	60.5 %		
Other chronic obstructive pulmonary disease	1		634	20.1 %	0.24	0.03
	2		597	18.9 %		
Emphysema	1		216	6.9 %	1	<0.001
	2		216	6.9 %		
Asthma	1		419	13.3 %	0.213	0.031
	2		386	12.3 %		
Acute kidney failure and chronic kidney disease	1		912	28.9 %	0.717	0.009
	2		899	28.5 %		
Human immunodeficiency virus [HIV] disease (B20)	1		29	0.9 %	0.788	0.007
	2		27	0.9 %		
Viral hepatitis	1		99	3.1 %	0.669	0.011
	2		105	3.3 %		
Disorders of lipoprotein metabolism and other lipidemias	1		1507	47.8 %	0.278	0.027
	2		1464	46.5 %		
Laboratory						
Variables	Cohort	Mean ± SD	Patients	% of Cohort	P-Value	Std diff.
Platelets [#/uL]	1	220.6 +/− 106.7			0.688	0.012
	2	221.8 +/− 101.5				
Hemoglobin [g/dL]	1	11.6 +/− 2.5			<0.001	0.145
	2	12.0 +/− 2.5				
Hematocrit [Volume Fraction]	1	35.1 +/− 7.1			<0.001	0.143
	2	36.2 +/− 7.1				
Erythrocyte mean corpuscular hemoglobin concentration [g/dL]	1	32.9 +/− 1.8			0.086	0.049
	2	33.0 +/− 1.5				
Erythrocyte mean corpuscular volume [fL]	1	90.8 +/− 7.4			0.368	0.026
	2	91.0 +/− 6.9				
Erythrocyte mean corpuscular hemoglobin [pg]	1	29.9 +/− 2.9			0.103	0.047
	2	30.1 +/− 2.7				
Erythrocytes [#/uL]	1	3.7 +/− 1.1			<0.001	0.144
	2	3.9 +/− 1.0				
Chloride [mmol/L]	1	102.2 +/− 5.4			0.42	0.023
	2	102.3 +/− 4.8				
Creatinine [mg/dL]	1	1.3 +/− 1.3			0.265	0.033
	2	1.3 +/− 1.5				
Erythrocyte distribution width [Ratio]	1	15.4 +/− 3.3			0.007	0.078
	2	15.1 +/− 3.1				
Urea nitrogen [mg/dL]	1	24.3 +/− 17.3			0.015	0.07
	2	23.1 +/− 16.2				
Glucose [mg/dL]	1	117.3 +/− 42.9			0.027	0.065
	2	120.1 +/− 44.6				
Potassium [mmol/L]	1	4.1 +/− 0.5			0.125	0.045
	2	4.1 +/− 0.5				
Sodium [mmol/L]	1	138.1 +/− 3.9			0.672	0.012
	2	138.2 +/− 3.6				
Bicarbonate [mmol/L]	1	26.4 +/− 4.2			0.975	0.001
	2	26.4 +/− 3.9				
Calcium [mg/dL]	1	9.0 +/− 0.7			<0.001	0.115
	2	9.0 +/− 0.6				
Basophils/100 leukocytes	1	0.5 +/− 0.5			0.503	0.02
	2	0.5 +/− 0.5				
Blood Pressure, Systolic [Hg]	1	127.5 +/− 24.1			<0.001	0.108
	2	130.1 +/− 24.1				
Blood Pressure, Diastolic [Hg]	1	70.4 +/− 14.0			<0.001	0.126
	2	72.2 +/− 14.9				
Eosinophils/100 leukocytes	1	2.3 +/− 3.0			0.128	0.045
	2	2.1 +/− 2.3				
Lymphocytes/100 leukocytes	1	21.1 +/− 13.4			0.579	0.016
	2	21.3 +/− 12.5				
Monocytes/100 leukocytes	1	8.2 +/− 4.1			0.54	0.018
	2	8.3 +/− 3.9				
Aspartate aminotransferase [U/L]	1	34.1 +/− 46.9			0.714	0.011
	2	33.7 +/− 36.1				
Alanine aminotransferase [U/L]	1	28.3 +/− 59.8			0.617	0.015
	2	29.1 +/− 32.4				
Leukocytes [#/uL]	1	8.2 +/− 5.2			0.029	0.07
	2	8.8 +/− 11.1				
Alkaline phosphatase [U/L]	1	99.5 +/− 76.8			0.792	0.008

(*continued*)

Cohort 1 (N = 3151) and cohort 2 (N = 3151) characteristics after propensity score matching [1]

Demographics						
Variables	Cohort	Mean ± SD	Patients	% of Cohort	P-Value	Std diff.
	2	98.8 +/− 73.5				
INR	1	1.5 +/− 0.8			<0.001	0.121
	2	1.6 +/− 1.1				
Bilirubin.total [mg/dL]	1	1.0 +/− 2.4			0.01	0.08
	2	0.8 +/− 1.4				
Albumin [g/dL]	1	3.6 +/− 0.7			<0.001	0.145
	2	3.7 +/− 0.6				
Neutrophils [#/uL]	1	27.0 +/− 313.2			0.832	0.006
	2	29.3 +/− 423.7				
Activated partial thromboplastin time (aPTT)	1	35.7 +/− 16.0			0.376	0.031
	2	35.2 +/− 15.8				
Prothrombin time (PT)	1	16.3 +/− 7.7			0.006	0.091
	2	17.1 +/− 10.6				
Magnesium [mg/dL]	1	2.0 +/− 0.4			0.095	0.063
	2	2.0 +/− 0.3				
Cholesterol [mg/dL]	1	158.5 +/− 49.4			0.873	0.006
	2	158.8 +/− 45.1				
Platelet mean volume [fL]	1	9.4 +/− 1.5			0.403	0.029
	2	9.4 +/− 1.6				
Cholesterol in HDL [mg/dL]	1	47.0 +/− 18.0			0.936	0.003
	2	47.0 +/− 17.6				
Triglyceride [mg/dL]	1	127.3 +/− 98.7			0.559	0.02
	2	125.5 +/− 80.6				
Cholesterol in LDL [mg/dL]	1	86.9 +/− 38.7			0.646	0.016
	2	87.5 +/− 36.3				
Phosphate [mg/dL]	1	3.6 +/− 1.0			0.816	0.009
	2	3.6 +/− 1.0				
Bilirubin.direct [mg/dL]	1	0.5 +/− 1.8			0.001	0.134
	2	0.3 +/− 1.0				
Hemoglobin A1c/Hemoglobin	1	6.3 +/− 1.4			0.689	0.016
	2	6.4 +/− 1.5				
Troponin I. Cardiac [ng/dL]	1	0.5 +/− 3.0			0.053	0.093
	2	0.9 +/− 5.7				
Lactate [mmol/L]	1	1.5 +/− 1.3			0.052	0.096
	2	1.4 +/− 0.8				
Bilirubin.indirect [mg/dL]	1	0.8 +/− 1.3			0.064	0.128
	2	0.6 +/− 0.7				
Gamma glutamyl transferase [U/L]	1	101.2 +/− 191.8			0.481	0.058
	2	114.7 +/− 269.9				
Natriuretic peptide.B prohormone N-Terminal [pg/mL]	1	5830.5 +/− 10,240.8			0.06	0.133
	2	4474.3 +/− 10,159.7				
Hepatitis C virus Ab [arbU/mL]	1	0.0 +/− 0.0			0.248	0.535
	2	475,934.9 +/− 1,259,205.2				
Left Ventricular Ejection Fraction (LVEF) (%)	1	53.3 +/− 17.8			0.861	0.016
	2	53.5 +/− 15.8				
Vital Signs						
Variables	Cohort	Mean ± SD	Patients	% of Cohort	P-Value	Std diff.
Oxygen saturation	1	88.0 +/− 18.6			0.454	0.038
	2	87.3 +/− 20.1				
Respiratory rate [breaths/min]	1	17.6 +/− 3.3			0.299	0.044
	2	17.4 +/− 3.0				
Heart rate [beats/min]	1	78.1 +/− 16.8			0.494	0.023
	2	78.5 +/− 17.0				
Body temperature [degF]	1	85.1 +/− 24.8			<0.001	0.171
	2	89.0 +/− 21.4				
BMI [kg/m^2]	1	28.5 +/− 7.3			0.032	0.063
	2	29.0 +/− 7.4				

arbU/mL, arbitrary unit per milliliter; beats/min, beats per minute; breaths/min, breaths per minute; degF, degrees Fahrenheit; fL, femtoliter; g/dL, gram per deciliter; Hg, mercury; kg/m^2, kilogram per square meter; mg/dL, milligram per deciliter; mmol/L, millimole per liter; ng/dL, nanogram per deciliter; pg, picogram; pg/mL, picogram per milliliter; s, second; U/L, units per liter; #/uL, number per microliter.

Appendix 3 Calculation of the Number Needed To Treat (NNT) to prevent clinically significant infection (CSI). The rate of CSI was lower in the group without antibiotics. We calculated the NNT according to the absolute risk difference between both groups.

	With antibiotics	Without antibiotics
Total patients	2737	2750
Number Needed to Treat for Clinically Significant Infection		
Number of clinically significant infections	15	10
Absolute risk	0.005	0.004
Absolute risk reduction (ARR)	0.002	

(*continued on next page*)

(*continued*)

	With antibiotics	Without antibiotics
Confidence interval	(−0.0015, 0.055)	
Number needed to treat	500	
Number Needed to Treat for Any Type of Drug Adverse Event		
Number of adverse drug events	26	26
Absolute risk	0.009	0.009
Absolute risk reduction (ARR)	0.000	
Confidence interval	(−0.0030, 0.0030)	
Number needed to treat	infinity	

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